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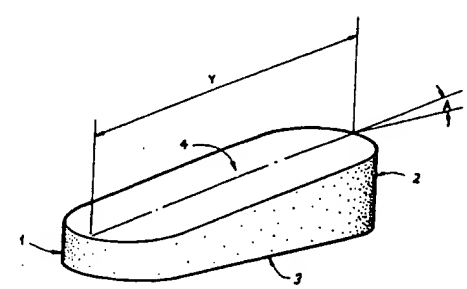
(54) Controlled release tablet.

(57) Compression gradient tablets are described which provide for controlled release of active ingredient.



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CONTROLLED RELEASE TABLET

TECHNICAL FIELD

This invention relates to compression gradient pharmaceutical tablets which are useful in providing controlled release of the active ingredient.

BACKGROUND

Controlled release of medicaments from pharmaceutical dosage forms has long been considered desirable. Controlled action dosage forms are generally more convenient for the patient than are non controlled release dosage forms, requiring fewer interruptions of daily routine and nighttime sleeping habits. Moreover, controlled release dosage forms provide for a more extended release of active ingredient within the therapeutic range than do multiple doses of conventional dosage forms. Controlled release is typically achieved by a variety of techniques such as coated slow release beads, multiple layered tablets, tablets with slow release cores, and tablets employing porous inert carriers or ion exchange resins.

Applicants have discovered that a differentially compressed tablet provides a unique controlled release profile of the active ingredient. The differentially compressed tablets of this invention are prepared by modifying the normally horizontal faces of tablet press punches (see Fig. 1a) so that either the upper or lower

punch face or both the upper and lower punch faces are sloped (see Fig. 1b). The sloped tablet punches produce tablets having sloped compressed faces as shown in Figures 2, 3 and 4. Tablets prepared in this manner will be differentially compressed, the thinner side being compressed with greater compressional force than the thicker side. The thinner side will be harder and will disintegrate and dissolve slower than the thicker side. Differentially compressed tablets dissolve slower and release active ingredient more slowly than do conventionally compressed tablets prepared from non-sloped tableting punch faces at comparable compressional force.

IN THE DRAWINGS:

FIG. 1 shows tableting punches:

(1a) a conventional tablet punch with a horizontal tableting face, and

(1b) a novel tablet punch with a sloped tableting face, the angle at which the punch face deviates from the horizontal is equal to the angle of inclination of a tablet produce therefrom,

FIG. 2 is a view in perspective of a tablet structure of this invention having a capsule-shaped peripheral side, an upper sloped compressed face, a thinner side, 1, compressed at more force than the thicker side, 2, the length of the inclined or sloped face, Y, and the angle of inclination, A, which measures the declination of the sloped face from the horizontal plane, and a lower horizontal compressed face, 3,

FIG. 3 is a view in perspective of a tablet structure of this invention having a capsule-shaped peripheral side, an upper sloped compressed face, a lower horizontal compressed face and beveled edges, and

FIG. 4 is a view in perspective of a tablet structure of this invention having a capsule-shaped peripheral side, an upper sloped compressed face, a lower horizontal compressed face and rounded edges.

SUMMARY OF THE INVENTION

The applicants have discovered that a differentially compressed pharmaceutical tablet will provide for controlled release of the active ingredient. The differentially compressed tablets of this invention are prepared using conventional tableting techniques modified only in the use of a sloped or slanted tableting punch face in place of the normally horizontal punch faces. The thinner side of the tablets of this invention are harder and release active ingredient more slowly than the thicker side which is softer. The compression gradient tablets of this invention provide for a more controlled release of the active ingredient than do conventional tablets.

DETAILED DESCRIPTION

Various factors influence the rate of release of active ingredient from the tablets of this invention including the active ingredient, the tablet excipients, the compression gradient and the shape of the peripheral side of the tablet. Drug substances which are readily soluble are expected to be released from a tablet of this invention more quickly than a drug substance which is only slowly soluble.

The pharmaceutical tablets of this invention can contain one or more drug substance as well as various tablet excipients. Although any drug substance can be administered by controlled release, for various reasons, certain drug substances when administered via controlled release formulations, offer little or no advantage over more conventional modes of administration. For example, controlled release administration is contraindicated or is of questionable value for a) drugs with long biological half lives (i.e., greater than 10 hours) such as chlorpromazine and thioridazine; b) drugs absorbed by active transport, as for example, quaternary ammonium compounds such as propantheline bromide; c) antibiotics such as penicillins and cephalosporins; d) drugs destroyed by first pass liver metabolism and/or metabolism in the gut wall such as ritodrine, salicylamide or lidocaine; and drugs that are naturally sustained release, for example, medicaments which are absorbed in body fat and subsequently are slowly released into the patients blood, such as chlorpromazine and thioridazine.

Medicaments which are suitable for use in the tablets of this invention include any drug substance or combination of drug substances which can be formulated in a solid dosage form and for which controlled release administration would be desirable. Suitable drug substances and their indications are, for example, acetaminophen, an antipyretic; aminophylline, a smooth muscle relaxant; amitriptyline HCl, an antidepressant; betamethasone phosphate, a glucocorticoid; brompheniramine maleate, an antihistaminic; buphenine HCl, a peripheral vasodilator; carbetapentane citrate, an antitussive; carbocromene HCl, a coronary vasodilator; chlorpheniramine maleate, an antihistaminic; chlorpromazine HCl, a tranquilizer; clonidine HCl; an antihyper-

tensive; codeine phosphate, an antitussive; diethylpropion HCl, an anorexiant; dihydroergotamine mesylate, a cerebral vasodilator; dextromethorphan HBr, an antitussive; diphylline, a bronchodilator; ergotamine tartrate, a vasoconstrictor; fenfluramine HCl, an anorexiant; ferritin, an antianemic; furosemide, a diuretic antihypertensive; heptaminol HCl, a cardiotonic; hydroquinidine HCl, an antiarrhythmic; ibuprofen, an anti-inflammatory; imipramine HCl, an antidepressant; indomethacin, an anti-inflammatory; isoxsuprine HCl, a vasodilator; isosorbide dinitrate, a coronary vasodilator; metformin HCl, a hypoglycemic agent; melperone, a neuroleptic; methscopalamine bromide, an antispasmodic; noscopine HCl, an antitussive; oxeladin citrate, an antitussive; papaverine HCl, a smooth muscle relaxant and cerebral vasodilator; pentazocine HCl, an analgesic; phenylephrine HCl, a sympathomimetic vasoconstrictor; phenylpropanolamine HCl, a sympathomimetic bronchodilator; potassium chloride, a potassium source for the treatment of hypokalemia; procainamide HCl, an antiarrhythmic; propranolol HCl, a beta receptor blocker, antihypertensive and antiarrhythmic agent; pseudoephedrine HCl, a bronchodilator and peripheral vasoconstrictor; theophylline, a smooth muscle relaxant, bronchodilator and myocardial stimulant; terbutaline sulfate, a bronchodilator; terfenadine, an antihistamine; and trihexyphenidyl HCl, an anti-Parkinsonian agent. Terbutaline, pseudoephedrine HCl, terfenadine and melperone are preferred drug substances.

Any amount of medicament can be formulated into the tablets of the present invention. Due to size limitations, the tablets of this invention should not exceed about 500 mg of medicament. Applicants prefer dosage forms having 300 mg or less of medicament. In

principle, there is no lower limit on the amount of medicament which can be formulated into the tablets of this invention. However, applicants prefer tablets having at least 0.1 mg of medicament. Preferred tablets of this invention will contain from 10 to 250 mg of active ingredient and will be comprise of from about 5 to 25 percent active ingredient by weight.

Applicants' tablets can contain one or more excipients in addition to the active ingredient. Although any pharmaceutical tableting excipient can be used, it is desirable that the chosen excipients render the tablet disintegration rate, at least moderately, sensitive to changes in compressional force to provide for a significant controlled release effect. Suitable tablet excipients for use in applicants' tablets are, for example, diluents such as lactose, hydrogenated vegetable oils, dextrose, mannitol, sorbitol, gelatin, acacia, dicalcium phosphate, tricalcium phosphate or monocalcium phosphate; binders such as sucrose, polyethylene glycol, polyvinyl acetate phthalate (PVAP), hydroxypropylmethyl cellulose, polyvinylpyrrolidone; disintegrants such as starch, karoya gum, methylcellulose, ethylcellulose, sodium alginate or bentonite; lubricants such as stearic acid, zinc, calcium or magnesium stearate, or talc, colorants such as FD&C dyes and lakes, and flavoring agents. (FD&C dyes: Food, drug and cosmetics dyes, approved by US Federal Drug Administrat

The compression gradient, the essential feature of the tablets of this invention, can be varied by changing the compressional force, the angle of inclination or the length of the sloped compressed face, Y, in Fig. 2. Greater compressional force produces harder tablets which dissolve more slowly and provide a more controlled release of active ingredient. The compressional force used in the tablets of this invention can be any force

sufficient to cause the tablet granulation to bind into a solid dosage form. Typically, tablets are compressed at from 150 to 3000 kg/sq.cm. In a preferred tableting process of the invention, the compressional force ranges from 500 to 1700 kg/sq.cm.

The angle of inclination of a tablet of this invention is the angle formed at the intersection of the sloped compressed face and a horizontal plane, angle A in Fig. 2 and is a measurement of the declination of the sloped face from a plane perpendicular to the axis of compression.

The angle of inclination of applicants' tablets can be any angle greater than 0 degrees of arc up to about 30 degrees of arc, preferably from 5 to 25 degrees of arc. In a preferred embodiment of the present invention, the angle of inclination is 10 degrees of arc. In another preferred embodiment of the present invention, the angle of inclination is 25 degrees of arc.

It should be kept in mind that the compressed faces and the peripheral sides of applicants' tablets need not be flat planer surfaces but may be convex, concave or otherwise rounded so long as one or both of the compressed faces are sloped. Where the tablet faces and sides are nonplaner, the angle of inclination can be determined by measurement of angle A, see Fig. 2, along planes which average the rounded surfaces of the compressed faces and peripheral sides. It should also be noted that the surfaces of the tablets of this invention can be embossed with various designs and insignia without materially affecting the ability of these tablets to provide controlled release of active ingredient. Moreover, the edges of the tablets of this invention need not be sharply angular but may be beveled as in Fig. 3 or rounded as in Fig. 4.

The peripheral sides of the tablets of the present invention can be any shape including, rod, capsule, oval, ovoid, circular, square, triangular and trianguloid. Because it is desirable that the length of the sloped compressed face, length Y in Fig. 2, be as long as possible in order to maximize the difference in compressional force from the thin tablet side, 1 in Fig. 2, to the thick side of the tablet, 2 in Fig. 2, certain peripheral side shapes are preferred. Among the preferred shapes are rod- and capsule-shaped sides. These shapes are preferred because the length of the sloped tablet face, Y in Fig. 2, and the resulting compression gradient, can be maximized for a given tablet weight. Typical capsule-shaped compression gradient tablets, having length Y maximized by sloping along the longer capsule-shape axis, are illustrated in Figs. 2, 3 and 4. Preferably in a capsule shaped tablet of this invention, the length of the sloped compression face, Y in Fig. 2, would be from 5 to 20 mm in length.

The compression gradient tablets of this invention are prepared in a manner analogous to procedures readily known by those skilled in the art for preparing conventional compressed tablets but using modified tableting punches. The tablet punches used in preparing the compression gradient tablets of this invention are sloped or slanted as shown in Fig. 1b. The declination of the sloped tablet punch is equal to the angle of inclination of the resulting compression gradient tablet. Either the upper or lower tableting punches or both the upper and lower tableting punches can be so modified. Additionally, the sloped tableting punch face may be modified to provide for convex, concave, or rounded edges or embossed designs and insignia. Tabletin is performed using conventional tableting machines

modified only by the use of the sloped face tableting punch.

The following examples illustrate the effect of a differentially compressed tablet on the release of active ingredient from a tablet dosage form.

EXAMPLE 1

Prepare conventional and compression gradient tablets of 500 mg each at 439.4 kg/sq.cm compressional force having the following composition:

d-Pseudoephedrine HCl	12%
Methocel E4M® (a hydroxypropyl methylcellulose sold by The Dow Chemical Company)	30%
Methocel K4M® (a hydroxypropyl methylcellulose sold by The Dow Chemical Company)	30%
Lubritab® (hydrogenated vegetable oil sold by Edward Mendell Company)	12.5%
Lactose NF	15%
Magnesium Stearate	0.5%

Using a conventional tablet and compression gradient tablets having an angle of inclination equal to 10 degrees and 25 degrees of arc, a dissolution test was performed using the United States Pharmacopeia Method I involving 0.1 N hydrochloric acid at 37°C and stirred at 50 rpm. The $T_{50\%}$ and $T_{90\%}$ values indicate the controlled release effect of the compression gradient tablets and indicate that the compression gradient tablet having a larger angle of inclination produce a

longer controlled release effect than the compression gradient tablet having a smaller angle of inclination. $T_{50\%}$ is the time required to release 50% of the active ingredient from the tablet. $T_{90\%}$ is the time required to release 90% of the active ingredient from the tablet.

	Conventional Tablet (min)	Compression Gradient Tablets Angle of Inclination 10° (min)	25° (min)
$T_{50\%}$	214	122	152
$T_{90\%}$	484	482	482

EXAMPLE 2

Prepare conventional and compression gradient tablets weighing 600 mg each at 439.4 kg/sq.cm (6250 p.s.i.) compressional force having the following composition:

d-Pseudoephedrine HCl	10.1%
Lactose (hydrous)	10.1%
Ethocel® (a solution of ethylcellulose in alcohol @ 22 cp. sold by The Dow Chemical Company)	.67%
Emcompress® (dicalcium phosphate sold by Edward Mendell Company)	77.1%
Sta Rx1500 Starch	1%
Magnesium Stearate	1%

Using the dissolution test of Example 1 the following results were obtained:

	Conventional Tablet (min)	Compression Gradient Tablets Angle of Inclination 10° (min)	25° (min)
$T_{50\%}$	47.9	--	63.5
$T_{90\%}$	152.0	--	363.0

EXAMPLE 3

Prepare conventional and compression gradient tablets weighing 600 mg each at 439.4 kg/sq.cm compressional force having the following composition:

d-Pseudoephedrine HCl	10%
Methocel® K100M (hydroxypropyl methylcellulose sold by The Dow Chemical Company)	10%
Emcompress® (dicalcium phosphate sold by Edward Mendell Company)	79%
Magnesium Stearate	1%

Using the dissolution test of Example 1, the following results were obtained:

	Conventional Tablet (min)	Compression Gradient Tablets Angle of Inclination 10° (min)	25° (min)
$T_{50\%}$	91.7	--	105
$T_{90\%}$	391.7	--	480

EXAMPLE 4

Conventional and compression gradient tablets having the composition set forth in Example 2 above were compressed at various pressures. The table below indicates the thickness of the tablets.

Compression Pressure (kg/sq.cm.)	Thickness (mm) Regular Tablet	Compression Gradient Tablet Thick side	Thin side
186	5.62	5.91	4.78
582	5.09	5.43	4.32
1246	4.80	5.16	4.01
1676	4.76	5.05	3.90

CLAIMS

1. A controlled release pharmaceutical tablet having compressed faces wherein at least one of the compressed faces is sloped to effect a compression gradient.

2. A tablet of claim 1 wherein the angle of inclination is from 5 to 25 degrees of arc.

3. A tablet of claim 1 wherein the angle of inclination is 25 degrees of arc.

4. A tablet of claim 1 wherein the angle of inclination is 10 degrees of arc.

5. A tablet of claim 1 wherein the peripheral side is capsule- or rod-shaped.

6. A process for preparing a compression gradient pharmaceutical tablet providing controlled release of the active ingredient by employing a tableting punch with a sloped face.

7. A process of claim 6 wherein the angle of inclination of the sloped tableting punch is from 5 to 25 degrees of arc.

8. A process of claim 6 wherein the angle of inclination of the sloped tableting punch is 10 degrees of arc.

9. A process of claim 6 wherein the angle of inclination of the sloped tableting punch is 25 degrees of arc.

10. A process of claim 6 wherein the resulting tablet has a capsule- or rod-shaped peripheral side.

11. A tableting punch as used in any of claims 6 to 10, characterized in that the tablet punch has a sloped tableting face.

12. A tableting punch of claim 11, wherein the angle of inclination of the sloped tableting face is from 5 to 25 degrees of arc.

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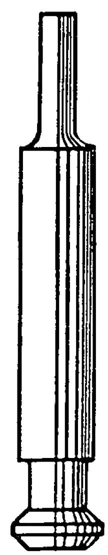

FIG 1a

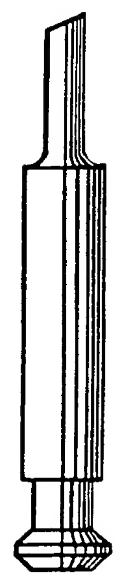

FIG 1b

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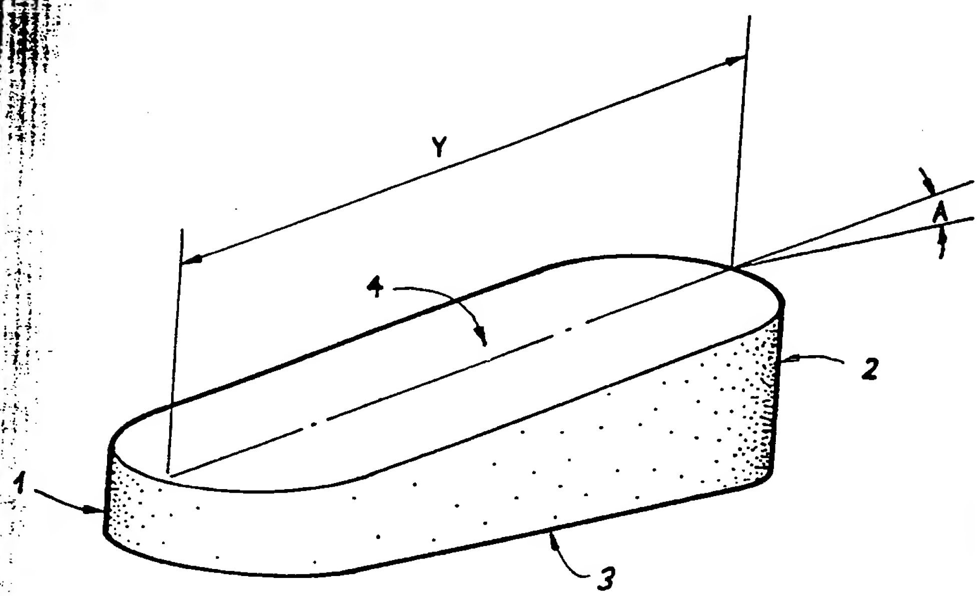

FIG 2

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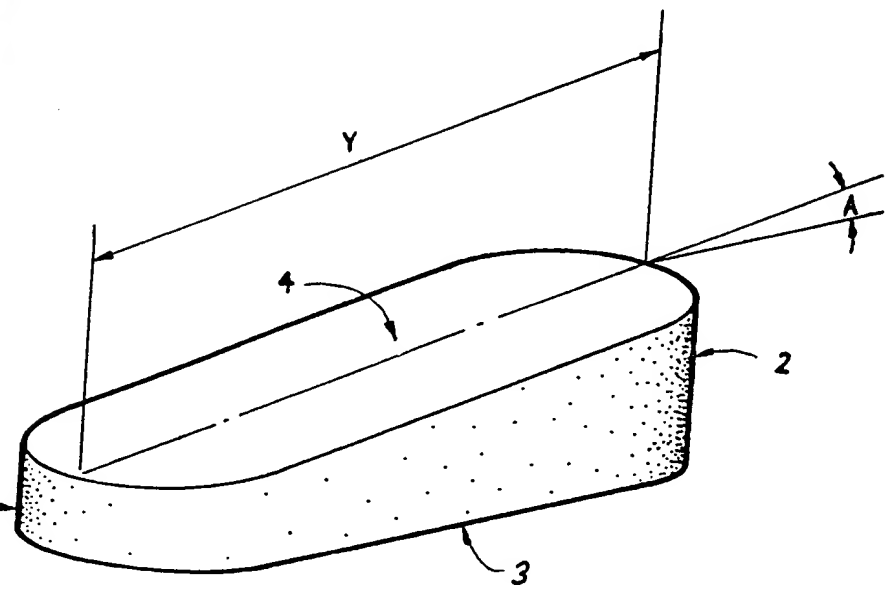

FIG 2

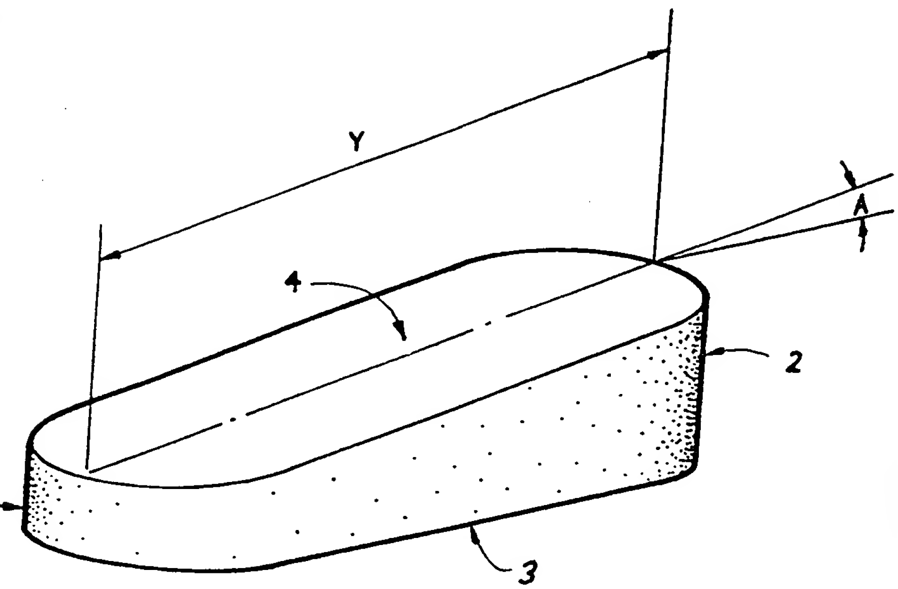

FIG 2

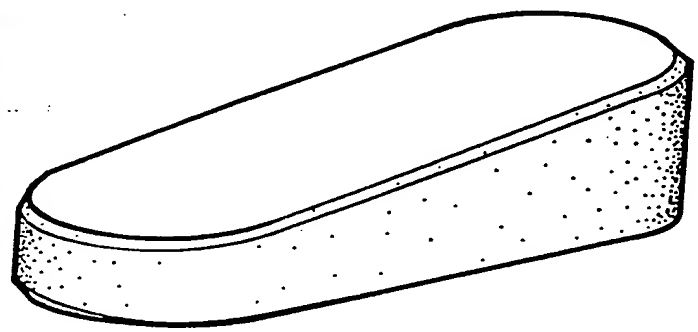

FIG 3

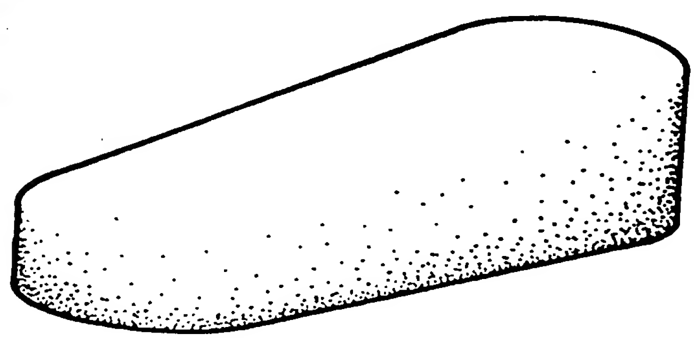

FIG 4

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MERRELL DOW PHARM INC *EP -126-453-A
19.05.83-US-496025 *(28.11.84)* A61k-09/22
Controlled release pharmaceutical tablet - is compressed with slant end punch to provide sloping face and compression gradient

B(11-C5, 12-M10, 12-M11) 2 069

C84-125570 D/S:- AT BE CH DE FR GB IT LI LU NL SE

TABLET CLAIMED

A controlled release pharmaceutical tablet has compressed faces with at least one (4) sloped to provide a compression gradient. The face angle of inclination (A) is pref. 5-25° and the tablet is produced using a punch with a face sloped at the required angle.

ADVANTAGE

The tablet becomes harder with decrease in thickness, so release is slower with increased hardness; and the arrangement provides a more controlled release than with conventional tablets. (18pp1358EDDwgNo2/4)
(E)ISR:- No Search Report.

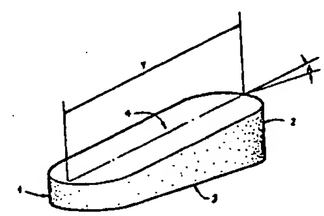

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EXHIBIT 311